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Pregnancy-PBPK models: how are biochemical and physiological processes integrated?

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Keywords

PBPK

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Pregnancy

Gestation

p-PBPK

toxicokinetics

Abbreviations

AAG, α 1-Acid Glycoprotein ; ADH, Alcohol Dehydrogenase ; ADME, Absorption, Distribution, Metabolism and Excretion ; CYP, Cytochrome P450 ; DDI, Drug-Drug Interaction ; DOHaD, Developmental Origins of Health and Disease ; Fup, Fraction unbound to plasma ; GA, Gestational Age ; GFR, Glomerular Filtration Rate ; GIT, Gastro-Intestinal Tract ; HBM-GVs, Human BioMonitoring Guidance Values ; HCT, hematocrit ; Kp, tissue-plasma partition coefficients ; NAT, N-acetyltransferase ; OAT, organic anion transporters ; OCT, organic cation transporters ; PBPK, Physiologically Based Pharmacokinetics ; PFAS, per- and polyfluoroalkyls substances ; P-gp, P-glycoprotein ; PK, Pharmacokinetics ; p-PBPK, pregnancy PBPK ; SULTs, sulfotransferases ; TK, Toxicokinetics ; UGTs, uridine diphosphate-glucuronosyltransferases

Abstract

Physiologically based pharmacokinetic (PBPK) modeling is used to predict the pharmacokinetic behavior of xenobiotics in humans. During pregnancy, anatomical and physiological parameters are modified leading to toxicokinetics' changes of substances in the body. Considering these physiological parameters change in the building processes of pregnancy PBPK (p-PBPK) model is essential to have accurate estimates of tissue/organ concentrations for the pregnant women but also for the fetus.

The review aims to summarize which specific processes are considered in the building of p-PBPK models and may be useful at the early stages of p-PBPK modeling.

To achieve this objective, a literature search focusing on anatomical, physiological, and biochemical parameters impacted by pregnancy was conducted. Most of the time, p-PBPK models do not include all the specific processes identified but only the most impacting ones on the global kinetics, depending mainly on the substance of interest. Allometric relations were identified to be classically included in the pregnancy models to describe the modifications induced by pregnancy to overcome the lack of data usually observed for the gestation. However, more and more data are gathered for pregnancy leading to the introduction of more data-based equations in PBPK modeling.

The most common strategy for p-PBPK development is based on the development of adult PBPK models that are then adapted to specific populations such as pregnant women. The adult PBPK model structure is modified to account for the pregnancy by adding specific compartments of fetal development and also specific compartments that are impacted during the pregnancy such as fat or mammary glands. Extrapolation of pregnant rat model is the other common strategy option used more specifically for environmental substances.

Overall, further data on maternal and fetal pharmacokinetics are needed to validate the xenobiotic exposure predictions during pregnancy, using for example *in vitro*, *in vivo* or *ex vivo* experiments.

1. Introduction

All along the pregnancy, women are exposed to numerous substances which may affect their health and/or the fetus' health and development [1, 2]. Fetal development is a period high of vulnerability to chemicals. In fact, exposure to chemical substances during critical periods of development may have short- and long-term consequences on the child's health. This concept has been proposed in the 'Developmental Origins of Health and Disease (DOHaD)' hypothesis [3, 4]. Numerous human biomonitoring studies have shown the wide exposure of pregnant women and their fetuses to numerous chemical families via the measurement of the concentration of chemicals in the maternal blood during pregnancy and/or in the umbilical cord at delivery [5-7]. In addition to environmental exposures, most pregnant women will likely be exposed to therapeutic drugs. Studies on medication intake during pregnancy showed that 64% of women ingest at least one medication in the course of their pregnancy [8, 9].

The fate of substances in the body, *i.e.* their toxico- or pharmacokinetics, during pregnancy can be altered by physiological and biochemical changes in the mother and by the development of the fetus [8-12]. These changes can lead to an underdosing or an overdosing of therapeutic drugs which can affect their safety or efficacy for both the mother and the fetus [13]. This can be especially true for narrow therapeutic index drugs for which variations of dose or blood concentration can lead to therapeutic failures. For example, the increase of renal filtration during pregnancy can lead to a faster elimination of antibiotics such as amoxicillin, which can affect its active concentration or time of efficiency [14]. In the case of lead, pregnancy conduct to a maternal bone lead release into the bloodstream, increasing the internal exposure and reaching the fetus through the placental barrier [15]. Knowledge of the evolution of the women's physiology during pregnancy is then decisive to assess their internal exposure to xenobiotics as well as for their fetuses. Due to the infeasibility of measuring toxicokinetic (TK) parameters in pregnant women and in the fetus, *in silico* methods can be used to evaluate pregnancy related changes on TK parameters.

PBPK models are mathematical models describing the kinetics of substances, based on their physicochemical properties and the physiology of the individual. These models divide the body into compartments, representing organs and tissues, in which the substances are absorbed, distributed, metabolized, and/or excreted. PBPK models consider both substance specific and physiological parameters and mathematical equations describe the behavior of the substance in the organism and how the body can affect them [16-19]. These models are used in both drug development and risk assessment of chemicals (they can be also referred to as PBTK models for Physiologically Based Toxicokinetic models). As PBPK models can integrate the characteristics of subgroups of the population to account for their influence on the kinetics of the compounds, they can be predictive tool to characterize internal exposure to xenobiotics in subgroups of the human population, *e.g.* in pregnant women and their fetus [20]. PBPK models for pregnant women are often referred to as p-PBPK models. The first p-PBPK models were published in the 1980s for pregnant rats [21, 22]. Many p-PBPK models developed before 2015 concerned environmental substances, but their development for pharmacological substances has known a rapid increase in the last decade. Through the years, p-PBPK models included more and more data-based equations that describe the evolution of the maternal and fetal physiology (*e.g.*, increase of certain organ volumes) and biochemistry (*e.g.*, modification of enzyme activities). Reviews such as the ones by Abduljalil, Furness [23] or Dallmann, Ince [24] gathered many data for these changes and provide equations to model developer that describe their evolution throughout the three trimesters of pregnancy.

This review is addressed for early reasoning on p-PBPK modeling development and aims to present how the physiological and biochemical evolutions in the mother and the fetus are considered in p-PBPK models. This work represents a repository of which physiological and biochemical processes are integrated into currently published p-PBPK models to guide model developers to the consideration of specific processes into their models.

Firstly, the literature search methodology to assess the extent of p-PBPK models existing will be presented. Secondly, the main development strategies of pregnancy PBPK models and how that impact parametrization will be addressed. After, models integrating these changes will be listed based on the ADME (Absorption, Distribution, Metabolism and Excretion) process affected by pregnancy. Then, the fetoplacental unit will be presented, with information about its integration into p-PBPK models, placental transfers and fetal distribution and metabolism. Next, an applications part will be presented, with concrete examples of p-PBPK models and their use. Perspectives and conclusion on this review will be finally addressed.

2. Bibliographic methods and bibliometric

2.1. Literature search

A systematic literature search was conducted to identify published human p-PBPK models published between 1980 and 2020 (Figure 1). PubMed was searched using the queries “Pregnancy AND PBPK” (150 hits) and “Placental transfer AND PBPK” (22 hits) in the titles, abstracts, or keywords of articles. Scopus was also searched with the queries “PBPK OR PBTK OR PBK OR PBK OR “physiological* based” AND model* AND pregnan* OR gestation OR prenatal OR fetus* OR foetus* AND human* OR women OR woman” (252 hits). In addition, the Toxnet Developmental and Reproductive Toxicology Database was used, with the request “PBPK” (136 hits). In total, 339 papers were gathered. Reviews and papers applying a PBPK model already published were excluded.

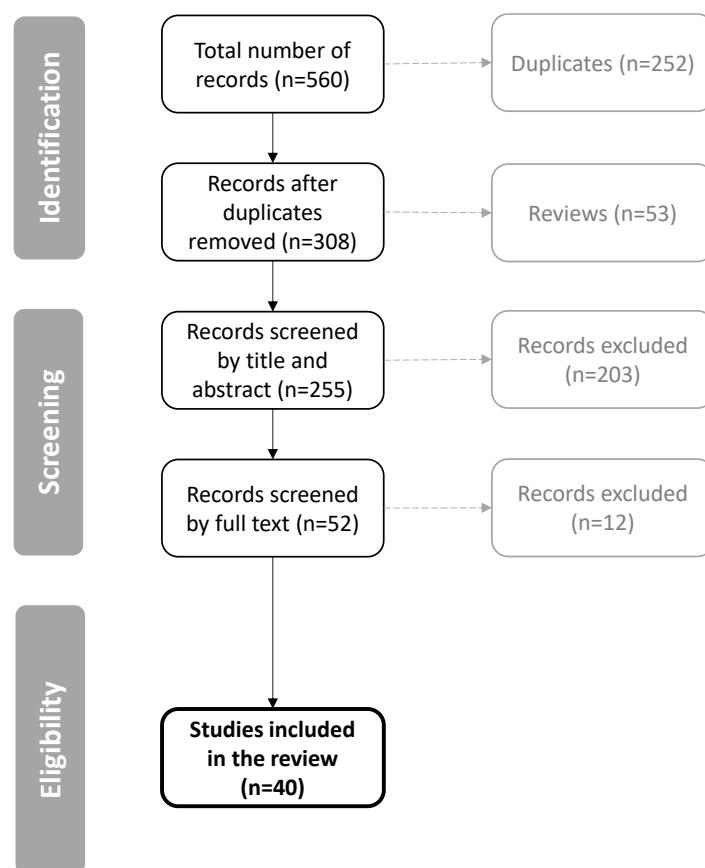


Figure 1. Diagram representing the literature search.

2.2. Bibliometric measurements

A total of 40 papers (listed in Annex A) concerned original human p-PBPK models. Among these models, 16 concerned environmental substances and 24 concerned drugs. Most of the p-PBPK models were developed for oral administration, which is the most common route of administration for drugs and food contaminants. Other routes as injection (intravenous or intramuscular) and inhalation, were also described in some models.

Figure 2 presents the 40 p-PBPK models by their publishing date. An increasing trend is observed in the last decade, demonstrating the high interest in p-PBPK development over the years.

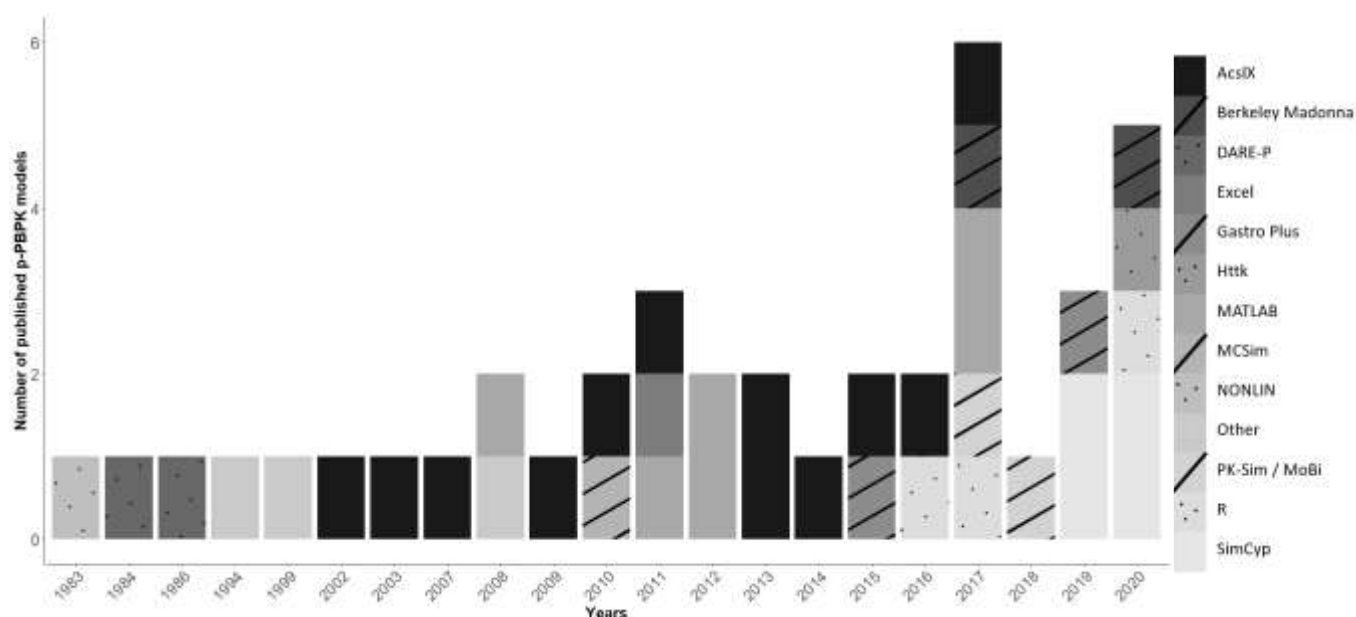


Figure 2. Number of published p-PBPK models from 1983 to 2020 (n = 40).

In Figure 3 are presented the different software used in the development of p-PBPK models. Mostly, AcslX®, MATLAB®, and Simcyp® were used to build p-PBPK models. Some of them offer a turnkey solution (Simcyp™, PK-Sim™...) whereas others require writing of the model (MCSim, AcslX...). Some software include p-PBPK models to predict exposure at different stages of pregnancy: Simcyp™ Simulator (Simcyp Ltd, Sheffield, UK, <http://www.simcyp.com>), GastroPlus™ (Simulations Plus Inc., Lancaster, CA, USA) and PK-Sim® (<http://www.open-systems-pharmacology.org/>). Most of the time, these turnkey software consider the physiological/anatomical parameters affected by pregnancy. They also integrate some changes concerning pregnant women in ADME processes.

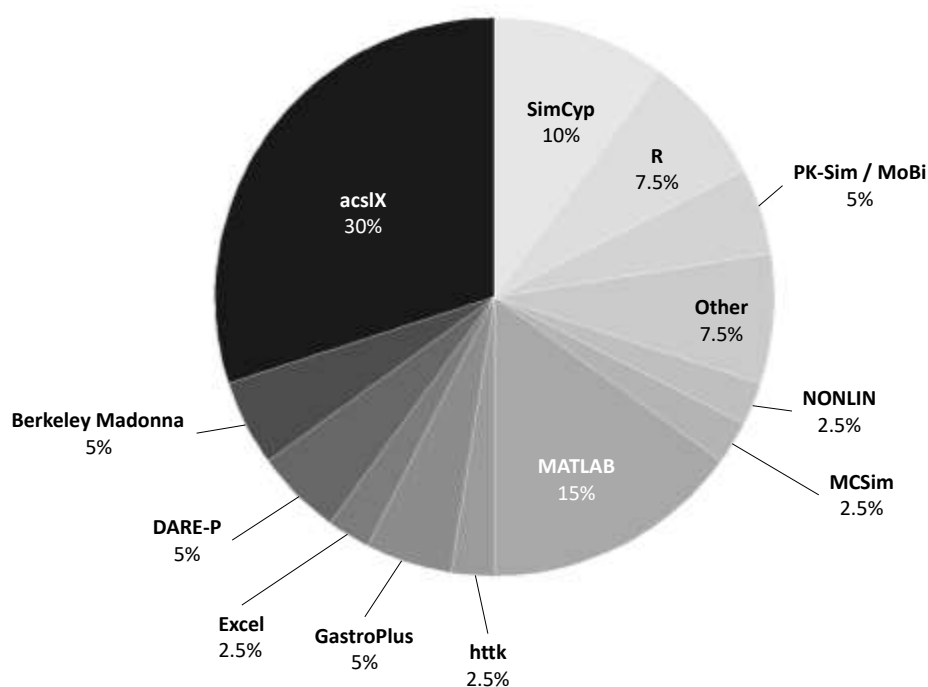


Figure 3. Software used for developing the original 40 p-PBPK models.

3. Strategies for p-PBPK model development

The strategy for p-PBPK development depends on the data context and on the objectives of the model, and consequently differs between drugs and environmental contaminants. The main difference lies in the data availability for their development and evaluation. For drugs, kinetic data in healthy volunteers are usually available to assess the reliability of a PBPK model. Then p-PBPK models can be adapted from these models developed for non-pregnant women by adjusting the physiological parameters and integrating the fetal development [25-29]. On the other hand, human kinetic data are rarely available for chemicals due to their potential adverse effects, except for high concern substances [30-32]. Then their model development cannot follow the workflow for drugs. Indeed, it is usual for p-PBTK models' development to lean on animals p-PBTK models [33, 34]. Often, a lack of data remains for these substances because of the difficulty to include the pregnant population into studies, and the use of animals (mainly rodents) models can provide data for estimates calculation [35-37]. The different strategies and steps involved in p-PBPK model development are provided in the following section (Strategy 1: Adaptation of human PBPK model to pregnancy and Strategy 2: Extrapolation p-PBPK model from animal to human).

3.1. Strategy 1: Adaptation of human PBPK model to pregnancy

The initial step for the first workflow consists in gathering data about *in vivo* PK data for the nonpregnant population and the physicochemical characteristics of the substance of interest and. A reference PBPK model is then built for adult women using all these data. If the model describes accurately the *in vivo* PK data observed, then it is transposed to pregnancy, otherwise, it is refined. To account for the pregnancy, the PBPK model structure is modified by adding compartments related to the pregnancy and fetal development, such as the breast, the uterus (endometrium and myometrium), the placenta (maternal and fetal sides), the amniotic fluid, the fetus, and the arterial and venous blood pool of the umbilical cord. Furthermore, the evolution of some physiological or biochemical parameters during pregnancy such as enzymes abundances, blood flows, and organ volumes are considered. Eventually, the p-PBPK model is evaluated by comparing the model predictions to available *in vivo* PK data. Figure 4 presents the general workflow of the p-PBPK model development when a non-pregnant adult PBPK model is available, as proposed by Dallmann, Solodenko [38].

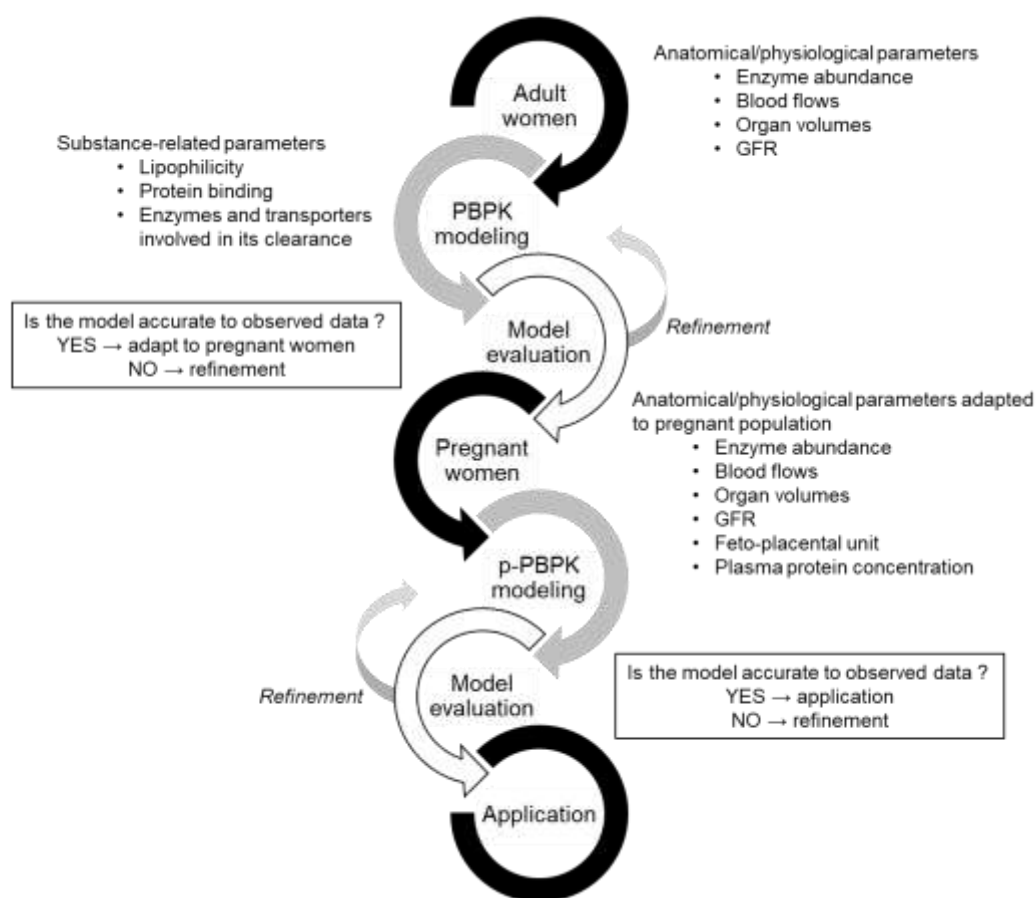


Figure 4. Representation of the first strategy for the development of pregnancy PBPK models, adapted from Dallmann, Solodenko [38]. GFR: Glomerular Filtration Rate

3.2. Strategy 2: Extrapolation p-PBPK model from animal to human

A second strategy was formalized based on the p-PBPK models gathered from literature. Figure 5 represents this 2nd workflow for p-PBPK model development when no human kinetic data is available (using rodents as an example): measured data from pregnant rat experiments are used to build a rat p-PBPK model. After its evaluation, the model can be extrapolated to the pregnant women population before its validation and application. Models such as the one developed by Loccisano, Longnecker [39], Takaku, Nagahori [40] and Merrill, Clewell [41] used this strategy. These models, developed for PFOS/PFOA, flumioxazin and perchlorate and iodide respectfully, were built as rat p-PBPK models using experimental pregnant rat data before being extrapolated to the pregnant women population and validated using literature data. To this end, physiological parameters are transposed to the pregnant

women using literature data (*i.e.* defining equations describing pregnant women physiology and their evolution during trimesters). For both Loccisano, Longnecker [39] and Takaku, Nagahori [40], tissue:plasma partition coefficients (K_p) were the same between rat and human p-PBPK models, as well as other chemical specific parameters such as the free fraction of chemical in tissues, fecal excretion constant, stomach-intestine transfer rate constant or diffusion coefficient parameters. For example, in the paper of Merrill, Clewell [41], the human volume of stomach capillary bed was scaled from rat data, as well as permeability coefficient and clearance values.

Few p-PBPK models based on virtual pregnant [42] population provided by specific software may not use neither workflows, such as the paper proposed by Abduljalil, Pansari [43], which use a virtual population from the software Simcyp® Simulator V19. Virtual pregnant population are based on gathered data from the literature and contains characteristics of pregnant women physiology'. Using virtual pregnant population allows the modeler to have a turnkey physiological parameters database and equations describing the physiology of pregnant women. However, these turnkey databases are not always available freely and are depending on specific software which can lead to the development of models that are mostly difficult to adapt to specific cases (e.g. exposure scenarios, removing or adding a new compartment).

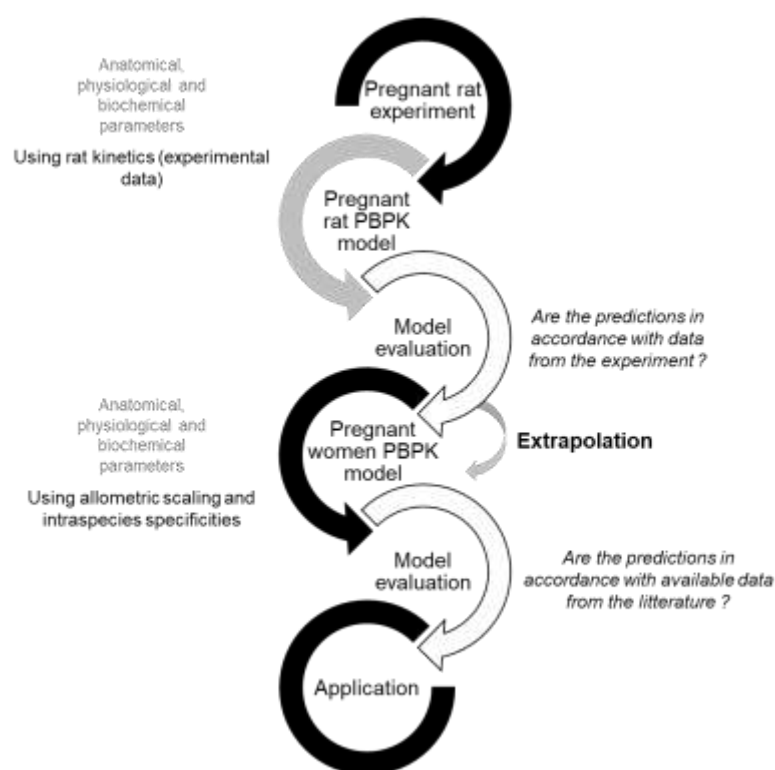


Figure 5. Representation of the second strategy for the development of p-PBPK models.

3.3. Methods for the inclusion of specific physiological parameters in the pregnancy models

Two main approaches have been used to integrate the physiological parameters adapted to the pregnancy in the p-PBPK models whatever the strategy selected. The first approach is based on allometric scaling, *i.e.* the scaling of physiological, anatomical or biochemical parameters by using experimental data from another species or population. For example, the bodyweight has been used to estimate physiological parameters in pregnant women, such as maternal organ and tissue weights and plasma flow rates, from values reported for non-pregnant women [44, 45].

The second approach is based on empirical equations derived from physiological data measured in pregnant women. That approach has become more and more popular thanks to the progress of the measurement techniques and the possibility to measure non-invasively some of the p-PBPK parameters (e.g., blood flow with imaging techniques). Recently, several reviews gathered data and the related equations for pregnancy [23, 46, 47]. The more data generated concerning pregnancy-related physiological or anatomical changes, the more p-PBPK models are specific and adapted to the pregnant population. For example, p-PBPK models integrated specific features for pregnant population

such as the hematocrit (HCT) level [26, 48-52], enzymes activities [29, 49-51, 53-55] or glomerular filtration rate (GFR) [48, 49, 56-60]. Abduljalil, Furness [23] conducted a literature search focusing on anatomical, physiological, and biochemical parameters impacted by pregnancy. Based on gathered data, equations were developed to provide resources to the building of p-PBPK models, for both the mother and the fetus. Numerous p-PBPK models use Abduljalil, Furness [23] equations to describe these variations during pregnancy [29, 57, 61]. Recently, Dallmann, Ince [46] provided an updated and extended database and conducted a meta-analysis to derive updated equations. Few p-PBPK models used these equations to describe accurately the changes happening in pregnancy [29, 62].

In Kapraun, Wambaugh [63]' meta-analysis, equations defining physiological changes observed in pregnant women are compared. They extracted equations from p-PBPK models from the literature and also calibrated different models before using the Akaike criterion to select the optimal model. In this paper, the repository of mathematical models for anatomical and physiological parameters provides a basis for PBPK models of human pregnancy and gestation and thus can help to support decision-making regarding p-PBPK models, for both pregnant women and their fetuses.

4. Integration of the pregnancy-induces changes affecting the ADME processes

Pregnancy is associated with several physiological changes that can affect the kinetic profile of compounds. Major changes occurring during this period and how they have been considered in the published p-PBPK model are presented thereafter. Most of these p-PBPK models were developed for the whole pregnancy, even if a few of them concerned only the second and/or third trimester [28, 50, 58, 61, 64-67]. Most anatomical and physiological maternal changes are emphasized in the last two trimesters of pregnancy, compared to the first one [10, 68]. In addition, the uteroplacental circulation is not demonstrated before the 12th week of pregnancy [69] and therefore might explain why some p-PBPK models only focus on the last trimesters. Several tables summarize how pregnancy affect the ADME processes and which p-PBPK models considered these changes.

4.1. Absorption

The oral administration was the most represented (75%) route of exposure in the 40 p-PBPK models identified. The other routes included the dermal exposure, the intravascular or intramuscular administration or the inhalation, which were present in respectfully 7.5%, 40% and 17.5% of the selected models. 30% of the selected models were considering multiples routes of exposure.

Both the lack of available data and little significance on the substances' kinetics led to an overall inconsideration of pregnancy related changes in absorption. Thus, the absorption integration in p-PBPK models is mostly the same as in the non-pregnant PBPK model.

4.1.1. Oral absorption

Oral absorption is driven by two fundamental processes: compound dissolution (or bioaccessibility for environmental compounds) and permeation by which the dissolved compound crosses the intestinal wall from the gastrointestinal fluid into the portal vein. Oral absorption can be modified during pregnancy. Few data are available and they can be conflicting from one source to another [10-12, 68]. Only few models accounted for absorption variations in pregnant women [58, 64].

During pregnancy, oral absorption can be affected by a slow stomach emptiness and a reduction of intestinal motility [70]. These changes can alter and delay the passage of a substance from the gastrointestinal tract into the systemic blood circulation which could ultimately affect both the peak concentration in plasma (C_{max}) and the time to C_{max} (T_{max}), respectively by increasing it and reducing it. During the 1st trimester, nausea is common and can affect the absorption of a substance by reducing the time of the substance presence into the stomach and therefore its time to reach blood circulation [70]. However, conflicting data concerning these parameters are found in the literature [13, 23, 71], and it is not clear if oral absorption is modified by the gastrointestinal changes observed during pregnancy [11].

In PBPK models, the gastrointestinal tract (GIT) can be represented either as a single compartment [59, 72] or as multiple compartments representing different sections of the GIT [28, 60, 73]. An advantage of using a compartmental absorption and transit model is taking into account the transit time, which can be modified during the pregnancy [8]. Atoyebi, Rajoli [64] included variations of the oral absorption of drugs in the course of pregnancy by incorporating gastric emptying and small intestinal transit flow. In addition, parameters such as the intestinal blood flow and gastric acid secretion are affected by pregnancy. However, these changes have not yet been included in p-PBPK models [11].

4.1.2.Dermal absorption

During pregnancy, the skin surface area increases, and its thickness is reduced. The total body water also increases, leading to a more hydrated epidermis and dermis which can affect the transdermal absorption, especially for hydrophilic compounds. The increase in the cardiac output leads to an increase in the skin blood flow which can also influence substance's absorption through the skin. However, little data is available concerning the dermal absorption in pregnant women [74]. In the p-PBPK model proposed by Sharma, Schuhmacher [52], the skin absorption of Bisphenol A, which can be found in cosmetics, is described according to skin blood flow and skin surface among others. Both parameters increase in pregnancy, inducing a faster absorption of the substance in pregnant women, and therefore a faster distribution to the blood.

4.1.3.Inhalation

In the case of an inhaled substance, its absorption might be enhanced due to the increase of the alveolar uptake. The tidal volume, which represents the volume of air breathed in or out during a normal breath, increases up to 45% during pregnancy [10, 68, 75, 76], due to both the increase of hormones and the enlargement of the chest wall during pregnancy. The previously mentioned anatomical changes can lead to a reduction of the absorbed dose of volatile anesthetics such as halothane [9, 70, 77] but has not been yet considered in p-PBPK model.

4.2. Distribution

During pregnancy, the distribution volume increases because of the growth of maternal volumes such as adipose tissue, mammary tissue, and pregnancy related organs, and of the development of the fetoplacental unit. The increase of body water, fat, plasma, and proteins necessary to the healthy development of the fetus [12, 78], in addition to amniotic fluid usually makes the bodyweight of pregnant women rise throughout the pregnancy, leading to increased drug accumulation and an apparent increase in the volume of distribution of certain drugs [11]. Abduljalil, Furness [79] and Dallmann, Ince [24] both presented repositories concerning physiological and anatomical evolution of the mother, based on measured data in pregnant women. For physiological parameters non affected by pregnancy, paper such as Brown, Delp [80] described values commonly used in PBPK modeling.

Pregnancy-related body weight increase, fat mass gain and plasma volume expansion affect the tissue distribution and are considered in the parameterization of p-PBPK models. Specific equations have been developed to describe the observed changes in tissue volumes as a function of the gestational age (GA), fetal weight or fertilization age using polynomial or Gompertz formulae [23, 46, 47, 51].

Pregnancy is also associated with significant changes in regional blood flows and drug binding, the two key parameters governing tissue distribution. During pregnancy, cardiac output and uterine perfusion, among others increase (up to 10-fold at term for the uterine perfusion) (**Table 1**). Both Brochot, Casas [81] and Chou and Lin [48] use a correction with hematocrit (HCT) to calculate the cardiac output, because of their substances of interest.

Pregnancy is also associated with major hematological changes, which can impact specific compound parameters used in PBPK models, such as the fraction unbound in plasma and the blood to plasma ratio. During pregnancy, the plasma volume rises to reach about 3.5L at the end of pregnancy [11], inducing hemodilution and a decrease in plasma protein concentrations. Differences in plasma protein concentrations between non-pregnant and pregnant subjects can lead to pronounced changes in the

fraction unbound in plasma (f_{up}) and subsequent changes in systemic drug disposition that should be incorporated in p-PBPK models [11, 12]. This is especially important for compounds with high degrees of plasma protein binding (>99% protein binding). Wood and Wood [82] described the binding of diazepam, lidocaine, and propranolol to α -1-acid glycoprotein and albumin in pregnant women, showing higher free fractions of these drugs compared to non-pregnant women. The efficacy and toxicity of compounds is usually related to the unbound drug concentration in plasma [83, 84], for drugs like phenytoin or tacrolimus and environmental contaminants as bisphenol A [85-88]. It is then important to account for the modifications in physiology that could affect the protein binding. f_{up} in pregnant women can be determined *in vivo* [50] or scaled from non-pregnant women to pregnant women using pregnancy-specific concentrations of plasma proteins estimated using published equations [56, 89, 90]. For instance, equations describing the concentrations of plasma proteins, albumin or α 1-acid glycoprotein (AAG) throughout pregnancy have been published [23, 46].

The hemodilution occurring during pregnancy will also affect the HCT values and the blood to plasma ratio. Different functions have been proposed to estimate the changes in HCT values in pregnant women based on different data set with inconsistent results [23, 46, 51]. According to the data collected, Abduljalil, Furness [79] and Gaohua, Abduljalil [91] consider that the HCT value decrease moderately throughout the pregnancy. On the contrary based on other published studies, Dallmann, Ince [24] and Brochot, Casas [81] (based on data from Cunningham [92]) estimate that the HCT decreases until 31 weeks of pregnancy, and then increases until the end of the pregnancy. Many p-PBPK models account for the evolution of the hematocrit and the albumin concentration using the equations proposed either by Abduljalil, Furness [23] or Dallmann, Ince [93] (**Table 2**).

In PBPK models, the tissue-plasma partition coefficients reflect the distribution of the compounds in tissues and are compound-specific. Partition coefficients depend on numerous physicochemical properties of the substance and the biochemistry of the cells. They can be measured experimentally or predicted using *in silico* tools (as quantitative structure-activity relationship). These tools often rely

on the composition of the tissues (fractional volumes of tissue water and lipid), and the F_{up} [94, 95]. The partition coefficient of each type of tissue can be estimated using different algorithms such as the ones developed by Poulin and Theil [95], Rodgers and Rowland [96] or Schmitt [94]. The algorithm selection relies mainly on the substance of interest and literature data available [97]. Pregnant women have higher plasma and body water volumes, inducing a lower plasma protein concentration compared to women (**Table 1**), which can influence K_p values of specific substances between non-pregnant and pregnant women.

Presently, K_p are the same between pregnant and non-pregnant women. Among the 40 models included in the literature search, none used pregnancy specific K_p for the mother. However, recently, Kapraun, Sfeir [98] evaluated a generic p-PBPK model using *httk* software package for which different K_p for mother and fetus. They applied the method of Schmitt [94, 99] and differing F_{up} have been considered for mother and fetus.

Abduljalil, Furness [23], Luecke, Wosilait [44], and Dallmann, Ince [24] described the evolution of the placenta's volume. They used equations to describe this increase in placental volume, either using gestational age, fetal weight, or fertilization age, respectively. All three equations are presented into Kapraun, Wambaugh [47] as part of the meta-analysis. These models for placental volume evolution during pregnancy are similar between them and with the model established in the meta-analysis, the cubic growth model [47]. Although this model is the most parsimonious, the similar model describing placental volume during pregnancy proposed by Abduljalil, Furness [79] is often used in p-PBPK models.

Table 1. Organ volumes and blood flows affected by pregnancy and their integration into p-PBPK models.

Parameter	Evolution during pregnancy	p-PBPK models accounting for this parameter
<i>Compartment volumes</i>		

Blood	↗	Alqahtani and Kaddoumi, 2015 ¹ Beaudouin et al., 2010 Gaohua et al., 2012 Luecke et al., 1994
Adipose tissue	↗ Increase of ~6L throughout pregnancy	Alqahtani and Kaddoumi, 2015 ¹ Beaudouin et al., 2010 Chou and Lin, 2021 * Codaccioni and Brochot, 2020 Gaohua et al., 2012 Luecke et al., 1994
Mammary gland	↗	Beaudouin et al., 2010 Chou and Lin, 2021 * Codaccioni and Brochot, 2020 Luecke et al., 1994
Sexual organs	↗	Alqahtani and Kaddoumi, 2015 ¹ Beaudouin et al., 2010 Luecke et al., 1994
Placenta	↗ Reach 0.7L at the end of pregnancy, increase during all trimesters	Alqahtani and Kaddoumi, 2015 ¹ Beaudouin et al., 2010 Chou and Lin, 2021 * Codaccioni and Brochot, 2020 Luecke et al., 1994
Amniotic fluid	↗ Reach 0.8L at the end of pregnancy, stable in T3	Alqahtani and Kaddoumi, 2015 ¹ Beaudouin et al., 2010 Chou and Lin, 2021 * Luecke et al., 1994
<i>Effects on blood flows</i>		
Uterine perfusion	↗	Alqahtani and Kaddoumi, 2015 ¹ Beaudouin et al., 2010
Cardiac output	↗ 30% during pregnancy	Alqahtani and Kaddoumi, 2015 ¹ Brochot et al., 2019 * Gaohua et al., 2012

¹ Equations coming from Abduljalil et al. (2012)

*Environmental substance(s), T1: 1st trimester of gestation, T2: 2nd trimester of gestation, T3: 3rd trimester of gestation

Table 2. Gestational age dependent distribution parameters and their integration into p-PBPK models

Parameter	Evolution during pregnancy	p-PBPK models accounting for this parameter
Plasma volume	↗ ~ 42%, reaching 3.5L at T3	Gaohua et al., 2012 Loccisiano et al., 2013 *

Plasma protein binding	\searrow Throughout pregnancy Albumin: -1% at T1, -10% at T2, -13% at T3	Alqahtani and Kaddoumi, 2015 ¹ Biesdorf et al., 2019 ¹ Codaccioni and Brochot, 2020 Freriksen et al., 2020 ¹ Gaohua et al., 2012 Zhang et al., 2018
Hematocrit	\searrow	Alqahtani and Kaddoumi, 2015 ¹ Chou and Lin, 2021 * Darakjian et al., 2019 ¹ De Sousa Mendes et al., 2017 ¹ Freriksen et al., 2020 ¹ Gaohua et al., 2012 Poet et al., 2017 * ¹ Sharma et al., 2018 * ¹ Zhang et al., 2018
	$\searrow \nearrow$	Brochot et al., 2019 * Codaccioni and Brochot, 2020

¹ Equations coming from Abduljalil et al. (2012)

*Environmental substance(s), T1: 1st trimester of gestation, T2: 2nd trimester of gestation, T3: 3rd trimester of gestation

4.3. Metabolism

Metabolism mainly occurs in liver but also in other organs such as intestines, lungs, kidney, skin or placenta. Hepatic clearance is dependent of hepatic blood flow and enzyme activity. Conflicting data concerning liver blood flow during pregnancy have been published [23, 46]. Due to these contesting data and the designs of the studies, liver blood flow is considered to be unchanged in the p-PBPK models during pregnancy [24, 79].

Metabolism includes phase I reactions (oxidation, hydrolysis, or reduction) and phase II reactions (conjugation). The major families of enzymes involved in metabolism are cytochrome P450 (CYP) for phase I reactions and uridine diphosphate-glucuronosyltransferase (UGT) and N-acetyltransferase (NAT) for phase II reactions. Several studies have shown that the activity of enzymes involved in the metabolism of xenobiotics can be modified during pregnancy [23, 46, 100]. Most of the data concerned the CYP enzymes and the three major families: CYP1, CYP2 and CYP3 involved in the metabolism of

most xenobiotics. Among them, 12 isoforms are responsible for the majority of phase I reactions [101]. The change is specific to each CYP450 isoform. For example, the activities of hepatic CYP2C9, CYP2D6, CYP2E1, or CYP3A4 are increased during pregnancy, increasing the clearance of specific substances involving these enzymes [28, 29, 50, 51, 54-56]. In contrast, CYP1A1/2 or CYP2C19 activities are lower in pregnant women than in non-pregnant ones, leading to a possible diminution in clearance and a longer residence time in the body [8, 11, 12, 102]. For some enzymes like CYP3A, CYP2C9, or CYP1A2, the induction or inhibition of their activity is linked to pregnancy hormones such as cortisol, estradiol, or progesterone [12]. For UGT isoenzymes, there are two major subfamilies UGT1 and UGT2. Increase in the activity of UGT1A4 and UGT1A9 has been reported during pregnancy [102].

An overview of pregnancy-induced changes on enzyme activities and their inclusion into p-PBPK models is presented in **Table 3**. Different strategies can be used to consider the pregnancy-related changes in enzymes activities in p-PBPK models to adapt hepatic intrinsic clearance. Most models [26, 28, 29, 54, 61] use gestational-dependent polynomial equations as proposed by Dallmann, Ince [24] or Abduljalil, Furness [79] to describe the increase (Eq. 1) or decrease (Eq. 2) of an enzyme activity during pregnancy. Generic second-degree equations are generally used such as follows (in %):

$$\text{Enzyme}_{\text{activity}} = \text{Enzyme}_{\text{act}_0} + a \text{ GA} - b \text{ GA}^2 \quad \text{Eq. 1}$$

$$\text{Enzyme}_{\text{activity}} = \text{Enzyme}_{\text{act}_0} - a \text{ GA} + b \text{ GA}^2 \quad \text{Eq. 2}$$

With $\text{Enzyme}_{\text{act}_0}$ expressing the enzyme activity before pregnancy (in %) therefore representing a normal activity in an adult (100%) and GA being the gestational age in weeks. Coefficients a and b are estimated from measured data. In most studies, the information of pregnancy-related changes in CYP activity used to define the values of the coefficients a and b comes from probe studies in humans performed to assess the activity of specific enzymes, instead of measuring their activity or expression. For instance, Hebert, Easterling [103] described the changes of CYP3A4 activity based on PK data collected after the administration of midazolam in pregnant women, with measurement in plasma

after its administration. This data of increased CYP3A4 activity during pregnancy can then be incorporated into p-PBPK models to describe more accurately metabolism of specific substances. Darakjian and Kaddoumi [26] used the same approach to provide an equation describing the CYP1A2 activity based on caffeine PK studies. In their paper, Freriksen, Schalkwijk [50] built a p-PBPK for Dolutegravir. This drug is metabolized mainly by UGT1A1 and partly by CYP3A4. During pregnancy UGT1A1 activity is found to be upregulated, like CYP3A4 activity. Since only few available data is available on UGT1A1 activity during pregnancy, Freriksen, Schalkwijk [50] proportioned this increase with the upregulation of activity of CYP3A4, which is more known.

Data concerning the activity of CYP2C8, UGT1A4, and UGT1A9 were gathered and expressed as an increase in their activity during pregnancy. However, CYP2C8 and UGT1A9 data were not transposed yet into an equation included into a p-PBPK model.

In the same way, data concerning the activity of NAT2 and cholinesterase were gathered and expressed a decrease in their activity, decreasing the apparent metabolism of substances [11, 23, 70, 71]. Yet, these data were not incorporated into p-PBPK models.

Table 3. Enzyme activities impacted by pregnancy and their consideration into p-PBPK models.

Enzyme	Enzyme activity compared to non-pregnant women	p-PBPK models accounting for this enzyme activity
<i>CYP</i>		
CYP3A4	↗ 50-100 %	De Sousa Mendes et al., 2017 ¹ Freriksen et al., 2020 Gaohua et al., 2012 Jogijaru et al., 2017 ¹ Ke and Milad, 2019 Pilari et al., 2011 Poet et al., 2017 ¹ Zheng et al., 2021
CYP3A5	↗ 60 %	Poet et al., 2017 * ¹
CYP2A6	↗ 54 %	Codaccioni and Brochot, 2020
CYP2B6	↗ 90% in T3	Chetty et al., 2020 Codaccioni and Brochot, 2020 De Sousa Mendes et al., 2017 ¹
CYP2C9	↗ 20 %	Alqahtani and Kaddoumi, 2015 Codaccioni and Brochot, 2020 Jogiraju et al., 2017 ¹

CYP2C19	↘ gradual throughout the pregnancy (-62% at T2, -68% at T3)	Almurjan et al., 2020 Atoyebi et al., 2019 Poet et al., 2017 * ¹
CYP2D6	↗ 50 %	De Sousa Mendes et al., 2017 ¹ Gaohua et al., 2012 Jogijaru et al., 2017 ¹
CYP2E1	↗ 80% in T3	Codaccioni and Brochot, 2020 Jogijaru et al., 2017 ¹
<i>UGT</i>		
UGT1A1	↗ ND	Freriksen et al., 2020 Jogiraju et al., 2017 ¹ Sychterz et al., 2021
UGT2B7	↗ 59%	Alqahtani and Kaddoumi, 2015

¹ Equations coming from Abduljalil et al. (2012)

*Environmental substance(s); T1: 1st trimester, T2 : 2nd trimester and T3 : 3rd trimester ; ND: not determined

4.4. Excretion

Excretion is the elimination of a compound from an organism, either as an unaltered form or as a metabolite. It commonly occurs through urine (kidney), feces or bile (liver). Based on a substance PK, some excretion pathways should be described more thoroughly in p-PBPK models as it can influence the predictions. In this section are presented how renal, biliary or other routes of excretion are affected (or not) by pregnancy and how modelers have adapted their pregnancy specific model.

4.4.1. Renal excretion

Renal clearance depends mainly on GFR and active tubular secretion and/or reabsorption. Increase in GFR, measured either by inulin or creatinine clearance, has been reported throughout pregnancy as compared with non-pregnant values and integrated in many p-PBPK models [28, 39, 48, 58-60, 81, 89, 104-106]. Based on published data, different equations describing GFR in pregnant women according to the gestational age were proposed by Abduljalil, Furness [23] and Dallmann, Ince [46]. Abduljalil, Furness [23] expressed the pregnancy-induced changes in GFR with an equation describing it as increasing until the 30th week of gestation before slightly decreasing for the last 10 weeks of gestation.

Models such as the one developed by Alqahtani and Kaddoumi [56] described the rise of 37% of the GFR during the 2nd trimester of pregnancy according to the gestational age, similar to the study by Abduljalil, Furness [79]. However, Dallmann, Ince [46] described the GFR based on data gathered using inulin and demonstrated a GFR increase until the end of the first trimester before stabilizing for the rest of the pregnancy.

A generic quadratic equation (Eq. 3) describing the rise of GFR during pregnancy could be written as, in mL/min:

$$\text{GFR} = \text{GFR}_0 + a \text{ GA} - b \text{ GA}^2 \quad \text{Eq. 3}$$

With GFR_0 being the glomerular filtration rate before pregnancy (mL/min) and GA corresponding to the gestational age in weeks. a and b are coefficients of GA are determined with literature data collected over all trimesters of pregnancy.

This quadratic model was used in the meta-analysis of Kapraun, Wambaugh [47] as the most parsimonious model for GFR. Abduljalil, Furness [79] also describes a very similar quadratic model, based on a curated data set. As an another example of the diversity of equations defining GFR, the *httk* R-package suggest using an allometric model based on the bodyweight of the woman, therefore increasing throughout pregnancy [107].

The main difference between these models is the dataset used to calibrate them. Each model presented in Kapraun, Wambaugh [47] are within the range of the curated dataset used. However, the predictions of the model developed by Abduljalil, Furness [79] are similar to the most parsimonious model and thus is the most commonly integrated in the p-PBPK models.

The other processes involved in renal excretion are tubular secretion and reabsorption due to membrane transport proteins. The proteins involved are organic anion transporters (OAT), organic cation transporters (OCT) and P-glycoprotein (P-gp). Less is known about the gestational changes in

renal tubular transporters. During pregnancy, renal transporters activity like OAT1, P-gp (P-glycoprotein), and OCT2 rises, which increases the active renal filtration of specific substances [11, 12]. Conflicting data concerning tubular reabsorption during pregnancy exists [108, 109]. For highly reabsorbed compounds, the changes on renal transporters should be considered as the excretion of the compounds could be lower than in non-pregnant women inducing a higher and longer internal exposure. For example, poly- and perfluoroalkyl compounds (PFAS) are known to be highly reabsorbed by transporter proteins in the proximal tubules of the kidneys but the variations in the transporters expression and activities have not been yet considered in the existing p-PBPK models describing the mechanism of reabsorption. However, Verner, Loccisano [59], Chou and Lin [48] and Loccisano, Longnecker [72]) described a maternal active reabsorption in kidneys of unbound PFAS in plasma, which is not specific to pregnancy and also present in the non-pregnant model for PFAS.

4.4.2. Biliary excretion

For the biliary excretion route, there is a gradually increase in serum bile acids during pregnancy, however this remains within the normal reference range [110], explaining its non-consideration in p-PBPK model building of compounds mostly eliminated via biliary excretion.

4.4.3. Other route of excretion

Other routes of excretion can be considered in p-PBPK models, such as blood loss at delivery. In their paper, Brochot, Casas [81] described a specific model developed for PFAS, which are highly bound to plasma proteins. The integration of blood loss, up to 10% of the maternal blood volume (representing a 500mL blood loss), affect the maternal plasma concentration in PFAS.

Finally, fecal excretion, sweat and exhalation can be considered as routes of excretion, however no literature data exist concerning a potential effect of pregnancy on them.

5. The fetoplacental unit

5.1. Representations of the fetoplacental unit in p-PBPK models

To predict exposure in the fetus, a fetoplacental unit is included in p-PBPK models with more or less complexity depending on the objectives of the model and the data available.

Figure 6 presents the different types of structures of the fetoplacental unit found in p-PBPK models, the percentage of each type within the selected models (40) and for each type of structure the distribution (in percentage) by trimesters of model's application.

Most of the selected models consider all trimesters of pregnancy. The only model concerning the 1st trimester of gestation has the simplest structure [111]. Models for which the trimesters of interest are not determined are the least recent publication.

In models developed to assess the impact of gestation on maternal PK, the fetoplacental unit is considered as one compartment (Representation A from Figure 6) [51, 56, 60]. However, when models are developed to investigate fetal exposure, the placenta is separated from the fetus. The fetus is not fully described in most of the papers. For example, if the aim of the study is to predict maternal PK and drug interactions in the mother, a precise description of the fetus could not be necessary. In many papers, the fetus is considered as one lumped compartment (Representation B from Figure 6) [33, 112, 113], and some models separate the fetal blood from the fetal organs and tissues (Representation C from Figure 6) [28, 59, 65, 72, 114]. However, depending on the aim of the paper, the addition of a complex fetoplacental unit could be required. More complex structures are also found with different compartments within the fetus (Representation D from Figure 6) [29, 44, 48, 52, 73, 115-117]. Most of these models take into account fetal organ compartmentalization according to the substance of interest and/or the target organ studied like brain [29, 52, 117] or liver [29, 48, 52, 73].

Abduljalil, Furness [23], Dallmann, Ince [24] and Kapraun, Wambaugh [47] derived equations from experimental data for the anatomical and physiological parameters of the fetus, such as placental volume, amniotic fluid volume, fetal mass, blood flows to the placenta or different fetal organs growth.

Recently, Abduljalil, Pan [118] described equations concerning fetal blood flows throughout pregnancy based on data gathered from the literature.

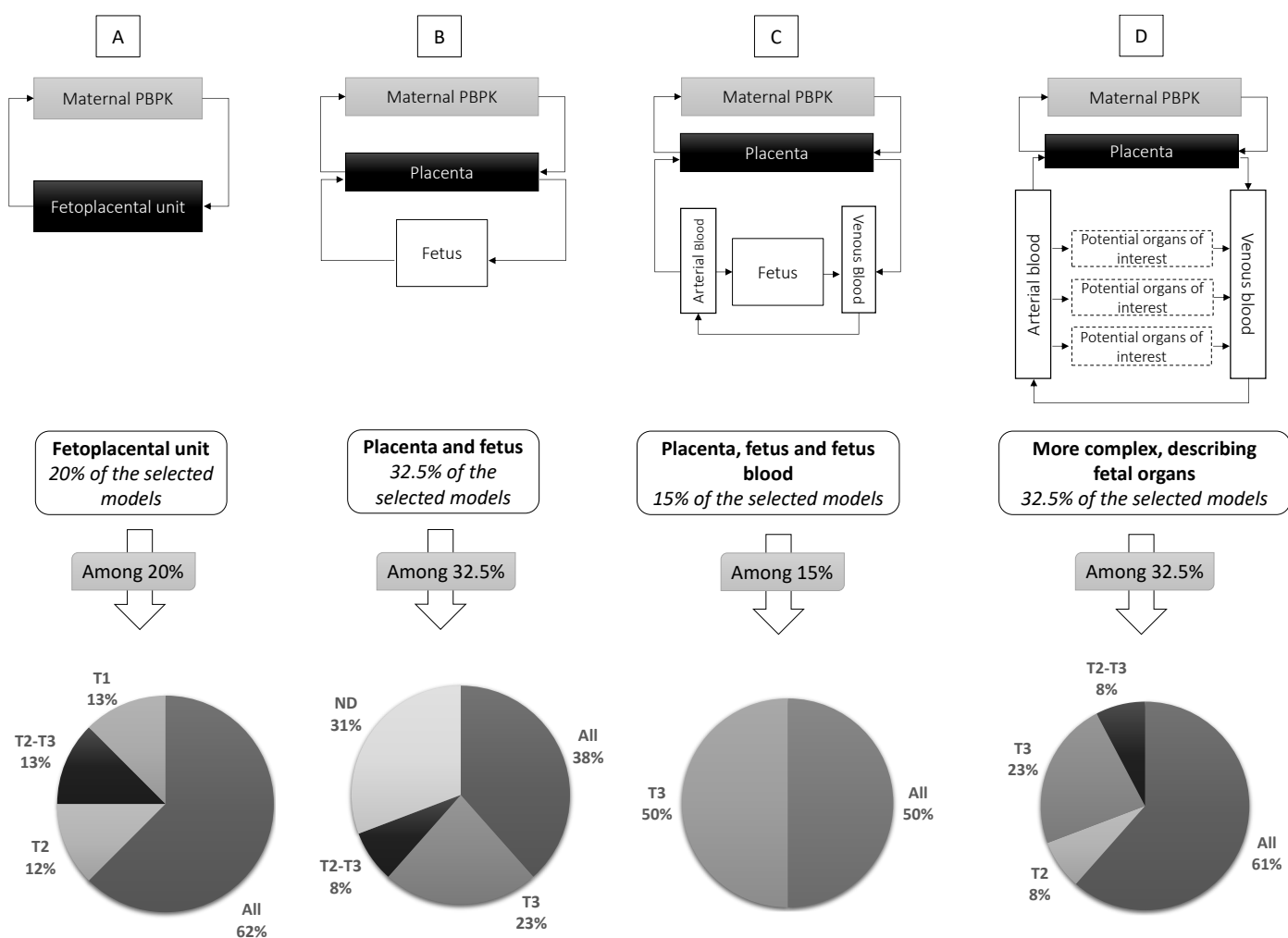


Figure 6. Schematic representation of the different types of fetoplacental unit in p-PBPK models and the percentage of each type of model among the selected models. Below each type of model are presented the trimesters of interest of each model type: every trimester (all), only the 1st (T1), 2nd (T2) or 3rd (T3) trimester, concerning the 2nd and 3rd trimesters (T2-T3) or not determined (ND).

5.2. Placental transfer

Placental transfer parameters as well as placental enzymes and transporters could be considered in p-PBPK according to the structure of the fetoplacental unit and available data. However, these processes are still little known and are therefore not included into p-PBPK models.

Transplacental transfer of compounds involves several mechanisms: passive diffusion, pinocytosis and facilitated and active transport via transporters. For hydrophobic molecules of less than 600 Da, passive diffusion is the predominant route [100]. On the other hand, protein-bound substances, and chemicals of large molecular weight hardly cross the placenta. For example, heparin and insulin are not transported to the fetus in significant amounts [70]. Almost all drugs, as mostly hydrophobic molecules, will ultimately reach the fetus through the placenta [100]. In some cases, this can be beneficial for the fetus to treat specific conditions through maternal blood, like fetal lung maturation with the administration of steroids to the mother [119].

The placenta expresses transporters, which can contribute to the transport of compounds from the maternal to the fetal bloodstream [12, 100, 119]. The major transporters are solute carriers (SLC) and ATP-binding cassette proteins (ABC) and transporter expression is gestational age-dependent [120]. The uteroplacental circulation was demonstrated to be established around the 12th week of gestation. Although diffusion of substances through tissues can happen before the second trimester of gestation, allowing exchanges between maternal and fetal circulation [47]. For passive placental permeability, transplacental transfers are described in p-PBPK models with two key parameters: the partition coefficient between the maternal and the fetal parts of the placenta and the transplacental transfer rates, that are bidirectional. To estimate the placental transfers, *in vivo* or *in vitro* data can be used. Still, a data gap remain, either from the maternal or the fetal side, impacting the building of accurate p-PBPK models [121]. Codaccioni, Bois [122] reviewed the different experimental and modeling methods to account for the placental transfers in p-PBPK models (*in silico* models, *in vitro* cell assays, *ex vivo* placental systems). These different methods can be used based on the substance of interest and data available in the literature. In most cases, placental transfers equations are based on gestational age, placental volume or surface [123]. Among the methods for assessing the placental transfers of xenobiotics, transplacental transfers data originates most of the time from *ex-vivo* human placenta perfusion experiments [118, 124]. For compounds for which active transporters are also involved in transplacental transfer, *in vitro* data can be integrated into the p-PBPK model as an IVIVE

(*in vitro* to *in vivo* extrapolation) approach to recreate transplacental transfers, such as data from the BeWo assay [125]. Recently, Lévêque, Tahiri [126] developed QSAR models to predict xenobiotics transfers through the placenta for many substances. These models could be used to estimate placental transfers based on the xenobiotic structure, to fill potential data gaps. To compensate for the lack of data in humans, placental transfer rate constants determined in rodents can be used [34, 72].

Placental metabolism can also affect the molar quantity transferred through the placenta. Indeed, both phase I and phase II enzymes are expressed in human placenta. Placental cytochrome P450, alcohol dehydrogenase (ADH), epoxide hydrolases, NATs and UGTs are few examples of enzymes expressed in the placenta [100]. Few models consider the activity of placental enzymes [50, 127-129]. In these models, substance specific placental clearances are taken into account, most of the time they are described as an overall organ clearance, and do not consider different enzyme expressions. In Liu, Momper [129], CYP3A4, UGT1A1 and UGT1A9 amount in the fetal part of placenta were included in the p-PBPK model.

5.3. Distribution and metabolism processes in fetuses

In p-PBPK models with a multi-compartmental fetal sub-model [72, 73], distribution in fetal tissues is modeled in the same manner as the distribution in the maternal compartments. Blood flows and partition coefficients are defined for fetal organs to describe the distribution of the substances in the fetus. Abduljalil, Jamei [130] published fetal age-based equations concerning fetal circulation through the trimesters of gestation, while considering fetal circulation specificities through the placenta. Fetal tissue:blood partition coefficients are usually assumed to be similar as for the mother.

In the fetus, immature phase I and phase II metabolism can appear 8 weeks post-conception, which can contribute to lower fetal exposure to the parent compound [70, 131]. CYP450 are the more important phase I enzymes and are predominately expressed in the liver [132, 133]. Data on enzymes expression in fetal compartments are limited in the published literature and are not available for all

enzymes. These enzymes activities remain low, and this associated with half of umbilical vein circulation passing through fetal liver to reach cardiac and cerebral circulations favor the issues of fetal drug accumulation [70]. Enzymes ontogeny in fetuses can happen at different stages of development, and therefore might explain why some enzymes are more expressed than others at different stages of growth. In the case of Bisphenol A metabolism in early-life stages, its sulfation is enhanced compared to its glucuronidation because of UGTs later expression compared to sulfotransferases (SULTs) [134-136]. In the PBPK models, when fetal metabolism is accounted, it usually concerns only the liver and other tissues. Some papers include specific data describing the activity of some enzymes in the fetus [28, 137, 138], such as CYP3A4, UGT1A1 or ADH. Despite functional fetal enzymes, the fetal liver is not effective enough to contribute to the maternal pharmacokinetics [12].

By 12 weeks of gestation, the amniotic cavity fills the entire uterine cavity [100]. Hydrophilic drugs may never reach fetal distributional equilibrium as the fetus rapidly excretes them into the amniotic fluid, which can be swallowed by the fetus [100]. In their model, Zhang, Imperial [117] considered the amniotic fluid to be swallowed by the fetus during gestation, therefore absorbing the substance of interest from the fetal intestine. Still, amniotic fluid is not often considered into p-PBPK models because data are difficult to obtain.

6. Applications

In the recent years, there have been extensive progress in the field of PBPK modeling demonstrating its use as a tool for exploratory translational research and regulatory decision-making, both in the pharmaceutical and nonpharmaceutical sectors [139]. Human p-PBPK models have been developed for numerous pharmaceutical substances and also for various environmental substances like metals [34, 116], pesticides [33, 61, 140, 141], bisphenols [52] or other persistent pollutants like dioxins, 1,3-butadiene and PFAS [72, 73, 81, 113, 142]. Among the applications of p-PBPK modeling, a few examples are highlighted in this review for drugs and environmental contaminants.

6.1. Drug development

In drug development, p-PBPK modeling can be used to optimize dose regimen, support evidence for efficacy, design clinical trial and ensure safety during pregnancy [143]. These models are widely used in drug development to predict the efficacy and potential toxicity for the mother and the fetus to compensate for the lack of *in vivo* data. It has been previously shown that if the drug is administered continuously during pregnancy, it can accumulate in the fetus and its effects may be significant for up to a few hours [144]. Additionally, they can support dose-finding before the first-in-human studies, describe metabolites disposition [54], or drug-drug interaction (DDI).

6.1.1. Fetal exposure

A p-PBPK model was developed by Mian, van den Anker [27] for acetaminophen and its metabolite, demonstrating lower acetaminophen plasma concentrations in pregnant women compared to non-pregnant women exposed to the same dose. Recently, Mian, Allegaert [145] integrated an *in silico* cotyledon perfusion model to the previous p-PBPK model developed for acetaminophen. This model was used to describe acetaminophen placental transfers and fetal pharmacokinetics. Indeed, besides optimizing maternal dose, p-PBPK models can also be used to monitor the exposure in the fetus: they can help assess transplacental transfers and fetal exposure to compounds throughout the pregnancy. Schalkwijk, Buaben [65] used an *ex-vivo* human cotyledon perfusion model to determine the placental clearance of an antiretroviral drug and thus the fetal exposure to this substance.

6.1.2. Dose adjustment

Throughout pregnancy, drug doses are often based on data coming from studies of non-pregnant subjects, which could conduct to under- or overdosing of drugs. In their paper, Abduljalil and Badhan [146] presented dose-adjusted drugs during pregnancy and examples of the use of PBPK models in dose adjustment recommendation during pregnancy within the context of DDI. Moreover, p-PBPK models can help optimizing dose to specific populations [53, 147].

For example, Darakjian and Kaddoumi [26] developed a p-PBPK model to describe caffeine exposure during pregnancy. Due to a reduction of CYP1A2 activity during gestation, caffeine exposure during pregnancy is increased compared to non-pregnant women, which can lead to an increased risk of miscarriage [148-150]. The application of this model could lead to a definition of maternal daily intake reference of caffeine throughout pregnancy.

6.2. Environmental chemicals

In risk assessment of environmental chemicals, p-PBPK models are used to simulate maternal predictions and to predict fetal internal exposure to a xenobiotic exposure [16, 29, 64]. Pregnancy PBPK models can be used to predict internal concentration in fetal compartments, for which data collection is not possible. Using predicted internal concentrations, estimations of parent compounds or metabolites accumulation in fetal organs during their development are possible. These predicted data allow a better understanding of maternal exposure effects at different trimesters of pregnancy.

6.2.1. Fetal exposure

Indicators of fetal exposure to PFAS from biomonitoring data gathered from mothers has been proposed using the model developed by Brochot, Casas [81]. This study highlighted different prenatal exposure patterns among the cohort. Other studies were more focused on the mother. Lumen, Mattie [151] used to determine if pregnant women's exposure to perchlorate could lead to a spectrum of disorders due to hypothyroidism in children. A biologically based dose-response model has been developed to predict maternal and fetal serum concentration of iodine and different thyroid hormones, in link with perchlorate exposure.

6.2.2. Risk assessment

In addition to increasing the accuracy of predictions, giving details to specific parameters of p-PBPK models can allow a better use of these models regarding risk assessment. Verner, Loccisano [59] demonstrated, with the use of a p-PBPK model, that important parts of the association between

prenatal PFAS exposure and reduced birth weight may be attributable to the variations in GFR during pregnancy. It suggests that GFR drives a portion of the association between prenatal PFAS exposure and low birth weight for data from large cohort studies, unlike results from smaller cohort studies, which were incoherent [59]. Changes in GFR during gestation can also affect the determination of guidance values in health risk assessment. Apel, Rousselle [152] presented strategies to derive human biomonitoring guidance values (HBM-GVs) for the general and occupational population. One of the strategies relied on a urinary mass balance approach, which can be affected by the modified GFR during pregnancy. Therefore, pregnant HBM-GVs can differ from the general population ones and specific values could be derived using p-PBPK models. Poet, Timchalk [61] developed Data Derived Extrapolation Factors for chlorpyrifos for pregnant women using a p-PBPK model coupled with pharmacodynamics model. These factors can be used in human health risk assessment, in the case of extrapolations, for chlorpyrifos and could be used for other chemicals with potential human exposure.

7. p-PBPK model quality and validation

Regulatory authorities have recognized the potential of PBPK modeling for biopharmaceutics applications [153, 154]. Guidance outlines the recommendation format and content to submit a PBPK model and are mainly focused on what information should be incorporated in the PBPK model documentation. Thus, the PBPK models for pregnancy have to follow these general recommendations. However, assessing the quality of p-PBPK models is a complicated task due the limited number of data that is available for building and verification. As proposed for evaluating the quality of the models specific for children [155], the following key aspects need to be considered also for evaluating p-PBPK models to have more insight into model quality: mechanistic uncertainty and quality/quantities of data.

As the processes affecting absorption, distribution and elimination are adapted in the pregnancy model, the uncertainty on the processes modified during pregnancy of the model increases. One key aspect to improve the confidence in p-PBPK models is to get meaningful human data to compare the maternal and fetal blood and tissue predictions to validate the model. Performing a sensitivity analysis

on the PBPK models is also an interesting tool to identify the specific mechanistic parameters that have the most impact on the internal maternal and fetal exposure (as performed in Personne, Brochot [156]).

The number and the quality of the data is the second key element for the verification that are variable, but mostly scarce [20, 121]. Indeed, the difficult access to data concerning the pregnant population impacts predictions of models, in need of accurate data to predict more accurately fetal exposure to chemicals [20, 102, 157]. In the case of pharmaceutical substances, more *in vivo* data are available concerning pregnant women, explaining increasing accuracy predictions with p-PBPK modeling. Yet, data concerning environmental substances remain sparse: some biomonitoring studies gather data concerning the pregnant population, through the sampling of urine, blood, hair, or cord blood [158-160]. These data lack can partly explain why p-PBPK models are not as accurate as adult PBPK models. For environmental compounds, animal p-PBPK models are generally the first step building human p-PBPK models. Gingrich, Filipovic [161] described fetal accumulation of bisphenols A and S in sheep, using a p-PBPK model, in addition to describing maternal exposure. This model was calibrated using animal data and contribute to a better understanding of bisphenolic compounds TK during pregnancy. In a same way, Personne, Brochot [156] characterized prenatal exposure to permethrin and estimated placental transfer of this compound in rats. The use of permethrin placental transfer could be extrapolated to the human to a better characterization of permethrin accumulation in the fetus and thus allow predictions of internal doses in fetal organs such as the brain, liver or blood. Based on these two examples, human p-PBPK models could be developed based on these data to describe human exposure to bisphenolic compounds and permethrin.

8. Perspectives

The application and use of p-PBPK models increase over the years, especially with the use of new data-based equations. Most of the models integrate physiological dynamic changes concerning cardiac

output, organs blood flow, and weight/volume as well as the growth of the fetoplacental unit. Also, pregnancy affects absorption, metabolism, and excretion in a gestational-stage manner. These gestational age dependent changes should be carefully considered in p-PBPK model development taking into account the ADME profile of the xenobiotic. Because of the complexity to measure experimental data in pregnant women, specific equations have been developed to express gestational age dependent changes on some ADME parameters. Regarding metabolism, CYP are the most important enzymes in xenobiotic elimination. Gestational changes in the activity of major CYP isoforms have been characterized using probe studies at different trimesters even if the majority of these data were obtained in the third trimester of pregnancy. Specific equations have been proposed to integrate these changes in p-PBPK models and adaptations in CYP activity should be performed according to the contributions from individual CYPs to total metabolic clearance. However, data are not available on all phase I enzymes involved in xenobiotic metabolism and even more for phase II enzymes. Further research is needed to complete the knowledge on gestational age changes in activities of metabolic enzymes as well as hepatic transporters.

For excretion, a specific attention should be done to compounds mostly excreted unchanged in urine as renal clearance is increased during pregnancy. Pregnancy increases GFR and specific equations have been proposed based on published data. However, pregnancy affects also renal transporters, which is important for highly reabsorbed compounds. There is a lack of data on the time course of changes in some renal transporters involved in secretion and reabsorption during pregnancy.

Drug-specific parameters are not always available, and assumptions are often made based on available data, especially for the fetus and the placenta. More data concerning fetal development will allow p-PBPK models to be more accurate concerning fetal exposure assessment. Regarding placental transfers, pregnancy induced changes in placental enzymes and transporters expressions are lacking and should be investigated to allow an accurate description and therefore accurate estimations.

Estimation of fetal exposure or internal concentrations in early stages of pregnancy, before the setting of blood circulation, could be debatable because of the numerous unknown parameters (volumes, blood flows...) in this window of time. This leads to uncertainties in establishing fetal volumes and/or blood flows in early pregnancy, which is critical for substances affecting embryogenesis.

Fetal organ predictions, for example in fetal brain, could be afterward linked to neurotoxic effects, with the use of data provided by cohorts. Therefore, associations of the effects of a substance at a given time in the pregnancy [59, 81, 161], or concerning the concept of DOHaD [3, 4] and its effects on development after birth could be developed. However, human fetal data remain sparse which can be a brake to accurate predictions concerning prenatal exposure to xenobiotics.

9. Conclusion

The development of p-PBPK modelling has increased over the past few years and will continue to increase as more data on specific physiological time-varying parameters during pregnancy are included in the models. However, further data on placental transfer and fetal metabolism are needed to validate the fetal exposure prediction to xenobiotics during pregnancy, through the use of *in vitro*, *in vivo* or *ex vivo* experiments. Nevertheless, fetal exposure assessment to substances with p-PBPK models are an important step towards understanding the exposure-effect relationship in the context of DOHaD and sensibility windows.

Competing interest

The authors declared no competing interest.

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Annex A

Authors	Substance(s)	Year of publication	DOI
Abduljalil et al.	Caffeine, theophylline, metoprolol, propranolol, paroxetine, midazolam, nifedipine and rilpivirine	2020	10.1007/s10928-020-09711-2
Alqahtani and Kaddoumi	Indomethacin	2015	10.1371/journal.pone.0139762
Andrew et al.	Midazolam	2008	10.1109/IEMBS.2008.4650448
Beaudouin et al.	Generic	2010	10.1016/j.yrtph.2010.01.005
Biesdorf et al.	Ziprasidone	2019	10.1111/bcp.13872
Clewell et al.	Methylmercury	1999	10.1111/j.1539-6924.1999.tb00427.x
Clewell et al.	Perchlorate and radioiodide	2007	10.1080/15287390600755216
Codaccioni and Brochot	Midazolam, theophylline, zidovudine, nevirapine, lamivudine, emtricitabine, cefuroxime, diazepam, ondansetron and metronidazole	2020	10.1016/j.taap.2020.115318
Dallmann et al.	Cefazolin, cefuroxime and cefradine	2017	10.1007/s40262-017-0538-0
Dallmann et al.	Caffeine, midazolam, nifedipine, metoprolol, ondansetron and diazepam	2018	10.1007/s40262-017-0594-5
Darakjian et al.	Caffeine	2019	10.1021/acs.molpharmaceut.8b01276
De Sousa Mendes et al.	Nevirapine	2016	10.1007/s40262-016-0457-5
Emond et al.	Dioxins	2016	10.1016/j.envint.2016.03.015
Freriksen et al.	Dolutegravir	2020	10.1002/cpt.1748
Gabrielsson et al.	Morphine	1983	10.1007/BF01061846
Gabrielsson et al.	Theophylline	1984	10.1007/BF01059275
Gabrielsson et al.	Pethidine	1986	10.1007/BF01059198

Gaohua et al.	Caffeine, metoprolol, midazolam	2012	10.1111/j.1365-2125.2012.04363.x
George et al.	Sertraline	2020	10.1038/s41540-020-00157-3
Gentry et al.	Isopropanol	2002	10.1006/rtph.2002.1540
Gentry et al.	Isopropanol, vinyl chloride, methylene chloride, perchloroethylene, nicotine, and TCDD	2003	10.1016/S0273-2300(03)00047-3
Horton et al.	Lithium	2012	10.1155/2012/352729
Ke et al.	Dexamethasone and betamethasone	2014	10.1002/cpt.1438
Loccisano et al.	PFOS / PFOA	2013	10.1080/15287394.2012.722523
Luecke et al.	Generic	1994	10.1002/tera.1420490205
Lumen et al.	Iodide and perchlorate	2013	10.1093/toxsci/kft078
Poet et al.	N-Methyl Pyrrolidone	2010	10.1093/toxsci/kfp264
Poet et al.	Chlorpyrifos	2017	10.1016/j.yrtph.2017.02.014
Schalkwijk et al.	Darunavir	2017	10.1007/s40262-017-0583-8
Sharma et al.	Bisphenol A	2018	10.1016/j.scitotenv.2017.12.023
Shintaku et al.	NSAIDs	2012	10.1111/j.1365-2125.2011.03921.x
Song et al.	Ceftazidime, cefuroxime, aztreonam, imipenem, ceftriaxone	2020	10.1002/bdd.2243
Sweeney et al.	Methyl iodide	2009	10.1080/08958370802601569
Takaku et al.	Flumioxazin	2014	10.1016/j.taap.2014.03.022
Valcke et al.	Chloroform, bromoform, TCE and PERC	2011	10.1016/j.yrtph.2010.10.008
Verner et al.	HCB, PCB-180, PCB-153	2008	10.1289/ehp.10917
Verner et al.	PFASs	2015	10.1289/ehp.1408837
Yoon et al.	Manganese	2011	10.1093/toxsci/kfr141
Zhang et al.	Drug X and Y	2017	10.1124/dmd.117.075192
Zhang et al.	Theophylline and zidovudine	2017	10.1124/dmd.116.073957